PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61L 27/00

A1

(11) International Publication Number: WO 95/13101

(43) International Publication Date: 18 May 1995 (18.05.95)

(21) International Application Number: PCT/NL94/00279

(22) International Filing Date: 8 November 1994 (08.11.94)

(30) Priority Data:
9301941 9 November 1993 (09.11.93) NL

(71)(72) Applicant and Inventor: DE GROOT, Klaas [NL/NL]; L. van Wijkplein 6, NL-2101 EL Heemstede (NL).

(74) Agent: SMULDERS, Th., A., H., J.; Vereenigde Octrooibureaux, Nieuwe Parklaan 97, NL-2587 BN The Hague (NL).

(81) Designated States: FI, JP, NO, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: A METHOD OF APPLYING A COATING OF A BIOACTIVE MATERIAL TO IMPLANTS

(57) Abstract

The present invention relates to a method of coating an implant substrate with a bioactive material represented by the general formula $Ca_p(PO_4)_q(CO_3)_r(OH)_s$, in which $p \geq 1$ and q, r and $s \geq 0$, and in which $2p = 3q + 2r + s$, wherein said substrate is placed in a solution in which at least calcium ions, preferably carbonate ions and, if required, phosphate ions, are present, after which the biocative material is precipitated from the solution on the substrate.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgystan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo			SE	Sweden
CH	Switzerland	KR	Republic of Korea	SI	Slovenia
CI	Côte d'Ivoire	KZ	Kazakhstan	SK	Slovakia
CM	Cameroon	LI	Liechtenstein	SN	Senegal
CN	China	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TG	Togo
CZ	Czech Republic	LV	Latvia	TJ	Tajikistan
DE	Germany	MC	Monaco	TT	Trinidad and Tobago
DK	Denmark	MD	Republic of Moldova	UA	Ukraine
ES	Spain	MG	Madagascar	US	United States of America
FI	Finland	ML	Mali	UZ	Uzbekistan
FR	France	MN	Mongolia	VN	Viet Nam
GA	Gabon				

Title: A method of applying a coating of a bioactive material to implants.

The present invention relates to a method of applying a coating of a bioactive material to implants that are to be fixed to skeleton parts. Furthermore, the method according to the invention relates to a new coating material.

Surgical implants comprising a bioactive material are known for the repair or reinforcement of skeleton parts, such as bones, joints and teeth. In this connection a bioactive material is a material effecting a specific biological response at the interface between an implant and a skeleton part. More in particular, there is obtained a bond between the skeleton tissue and the implant material. It is self-evident that the growth of an implant into a skeleton tissue is of great advantage. It is highly important as regards the increase in clinical function.

Thus, it is known that silicate glass, specific ceramic glass compositions as well as silica layers, titania layers and zirconia layers prepared using the sol-gel method are capable of chemically bonding to bone tissue. More in particular, in a physiological environment an apatite layer grows onto surfaces of these materials. This method takes place both in vivo and in testing systems using simulated body fluids. Apatite is a bioactive compound ensuring a bonding between the above glassy materials and living skeleton tissue. This is extensively described in Panjian Li, *In vitro* and *In vivo* Calcium Phosphate Induction on Gel Oxides, PhD Thesis Leiden University, Offsetdrukkerij Haveka B.V., Alblasserdam, The Netherlands (1993) and in Panjian Li et al., J.Am.Ceram.Soc. 75 (1992), 2094-2097.

It is further known from the survey article "Medical Applications of Calciumphosphate Bioceramics" by K. de Groot in Ceramics International 19 (1993), 363-366 that ceramic articles made of calcium phosphate salts can be successfully used to replace and reinforce bone tissue. It is known both to produce implants completely from such ceramic materials and to

apply a coating of such a material to a substrate used as implant, e.g., stainless steel.

Implants made of only bioceramics and bioglass, e.g., implants from calcium phosphate salts, possess strong compression properties, but are weak under stress and have a poor fatigue strength. Therefore, such massive implants can be clinically applied only in places where no high tensile strengths occur. An example of a clinical application of an implant of only calcium phosphates is the replacement of middle ear bones.

Implants of a strong material coated with hydroxyapatite or other bioactive compounds related to calcium phosphate actually possess a high strength. Coatings of calcium phosphate salts and in particular of hydroxyapatite can be applied to substrates in various ways.

The contribution by Paul Serekian in Hydroxylapatite Coatings in Orthopaedic Surgery, edited by R.G.T. Geesink and M.T. Manley, Raven Press, Litd., New York (1993), 81-87 discusses the advantages and disadvantages of, inter alia, plasma spraying, flame spraying, dip coating, electrophoresis and magnetron sputtering. The most conventional coating method is plasma spraying.

EP-A-0 450 939 describes a method of applying a hydroxyapatite coating to implant substrates. This method comprises combining a soluble calcium ion source and a soluble phosphate ion source under conditions leading to controlled nucleation and modulated crystal growth. In essence, one solution is injected into the other, which has the result that at the interface of both solutions a supersaturation situation arises from which whiskers of calcium phosphate develop. Then a flow is induced, in consequence of which the whiskers reach and cover the surface to be coated.

EP-A-0 130 916 and EP-A-0 042 783 describe complicated methods which comprise applying a mist of particles containing calcium ions and orthophosphate ions to a substrate.

An important disadvantage of all these known methods is that the methods are laborious and complicated. There is

therefore a need for a simple method of coating suitable implant substrates.

Bioactive compounds bind to skeleton parts, because these compounds strongly resemble the mineral phase of skeleton tissue in structure. In recent years the calcium phosphate system, and in particular hydroxyapatite, have been extensively studied. Hydroxyapatite is a naturally occurring mineral constituting the most important mineral component in bones and in dental enamel. Besides, in this connection the calcium carbonate system and carbonate-containing hydroxyapatite has also been studied.

Bone minerals consist mainly of a complex mixture of calcium ions, phosphate ions, carbonate ions, and hydroxyl ions, while potassium ions and sodium ions are also present. It is assumed that a series of salts of the general formula $Ca_p(PO_4)_q(CO_3)_r(OH)_s$, in which $p \geq 1$ and q, r and $s \geq 0$, and in which $2p = 3q + 2r + s$, can bind to skeleton parts, when these salts are present in the form of a solid implant or as a coating material for other, e.g., metal implants. If p=10, q=6, r=0 and s=2, the above formula gives the structural formula of hydroxyapatite; if p=1, q=0, r=1 and s=0, calcium carbonate is shown; and if, e.g., p=9, q=5, r=1 and s=1, a carbonate-containing hydroxyapatite is obtained.

There has now been found a simple method by which the problem of the known coating methods is solved. This simple method is based on the mere well-known fact that hard water often forms precipitates. These precipitates usually cause a problem. The precipitates formed can only be removed with difficulty, owing to the excellent bond to the materials on which they precipitate. In particularly, reference is made to incrustation in kettles and pans, the occurrence of scale in, e.g., washing machines, etc. The precipitates consist mainly of calcium carbonate complexes. According to the invention this usually disadvantageous effect is inventively utilized.

The invention relates to a method of coating an implant substrate with a bioactive material represented by the general formula (I) $Ca_p(PO_4)_q(CO_3)_r(OH)_s$, in which $p \geq 1$ and q, r and

$s \geq 0$, and in which $2p = 3q + 2r + s$, which substrate is placed in a solution in which at least calcium ions, preferably carbonate ions and, if required, phosphate ions and/or a source for hydroxyl ions are present, after which the bioactive material is precipitated from the solution on the substrate.

Besides, International Patent Application 93/07912 describes a bioimplant obtained by immersing a base material to be coated in a saturated or supersaturated solution of hydroxyapatite. The base material has been previously provided with an organic polymer containing sulfonic groups or carboxyl groups. In the method according to the invention it is not necessary to first provide the implant to be coated with such an organic coating.

In the method according to the invention the presence of calcium ions in a solvent is essential. In a number of preferred embodiments the presence of carbonate ions or hydrogen carbonate ions will further be utilized for the precipitation reaction.

On the solvent the requirement must be imposed that calcium ions, carbonate ions and phosphate ions can be present therein. In a preferred embodiment of the method according to the invention the solution used is an aqueous solution, preferably water.

Normally, in the method according to the invention the starting solution will be a solution containing calcium ions. Hydrogen carbonate ions can be added to this solution in the form of a soluble hydrogen carbonate salt or formed in situ from a soluble carbonate salt or from CO_2 gas passed through.

As is generally known, the incrustation referred to above is formed when hard water containing calcium ions is boiled in the presence of carbon dioxide. Carbon dioxide forms hydrogen carbonate ions in water. By boiling the water, decomposition of (a part of) these hydrogen carbonate ions occurs, after which the poorly soluble calcium carbonate is formed.

In formula form this reaction proceeds in, e.g., water as follows:

$$Ca(HCO_3)_2 \xrightarrow{\text{(increased temperature)}} CaCO_3(\downarrow) + CO_2(\uparrow) + H_2O$$

Hydrogen carbonate ions give a weakly acid pH in water. The escape of (a part of the) carbon dioxide gas will cause the pH of the remaining solution to increase or, in other words, the concentration of OH^- ions will increase.

When in a solution having calcium ions and (hydrogen) carbonate ions phosphate ions are present as well, these will also precipitate when the pH increases. This may be represented by means of the following (incomplete) reaction equation:

$$Ca^{2+} + HPO_4{}^{2-} + H_2PO_4{}^- + HCO_3{}^- \rightarrow CO_2(\uparrow) + Ca_p(PO_4)_q(CO_3)_r(OH)_s(\downarrow)$$

Depending on the ion concentrations and pH of the solution, a precipitate of a compound of formula (I) having any desired value for p, q, r and s can be obtained. By way of experiment, a skilled man can simply determine the process conditions for precipitating a desired coating composition. Preferably, a bioactive material is precipitated in which the p/q ratio ranges between 1 and 2.

More in particular, in the literature the solubility products of the different calcium-carbonate-phosphate salts are known as a function of the temperature and pH (see, e.g., F.C.M. Driessens, Formation and Stability of Calcium Phosphates in relation to the Phase Composition of the Mineral in Calcified Tissues, <u>in</u> Bioceramics of Calciumphosphate, K. de Groot editor, CRC Press, 1984). Besides, it is generally known that according as the concentration of ions in a solution increases the following conditions may occur: undersaturation; supersaturation or the formation of a metastable state; and precipitation. These three stages can also be created by, e.g., increasing the temperature and/or pH.

The manner in which, according to the invention, the coating layer is precipitated from a solution containing at least calcium ions and carbonate ions is not critical. On the other hand, when using the method according to the invention, it is most effective if the starting solution is in the

metastable state. The simulated body fluid described in the above publications by Panjian Li is very satisfactory. This simulated body fluid has an ion composition resembling the ion composition of fluids present in the body, such as blood and lymph. In essence, a suitable precipitate can be deposited from such a metastable fluid on a substrate by placing the substrate in this solution and maintaining it therein for some time, e.g., some days. Methods are preferred, however, in which by means of a change of temperature or a change of pH a precipitate is obtained on a substrate deposited in the metastable solution. Such methods are better controllable, regulable.

In one preferred embodiment the solution is heated so as to precipitate the bioactive material on the substrate. Although this depends on the ion concentrations in the (metastable) solution, an increase in temperature by 50°C will generally be sufficient to precipitate the desired calcium salt. This method is comparable to the incrustation in a kettle.

In another embodiment the substrate (partly) immersed in the solution is heated so as to precipitate the bioactive material thereon. This method is comparable to the formation of scale on a heating element in, e.g., a washing machine. Depending on the ion concentrations in the solution, a temperature difference between the substrate and the solution of about 50°C will generally be sufficient for a desired precipitation.

In yet another embodiment caustic soda is added to the solution so as to precipitate the bioactive material on the substrate. This embodiment is comparable to known methods for softening (waste) water. In these softening methods, e.g. described in the publication Abscheidung von Calciumphosphaten aus Abwasser durch Kristallisation im Wirbelbettreaktor by E. Eggers and J.C. van Dijk, which publication was read on November 28, 1986 at the Symposium Entfernung von Phosphaten aus Abwässern und Nutzbarmachung von Klärschlammen held at Frankfurt/Neu-Isenburg 2, FRG, caustic soda is injected into a

flow of hard water. Thus, a metastable solution is formed, which, after passing through a fluidized bed of, e.g., grains of sand, is softened. In the method according to the invention the basic solution added may in principle be any basic compound. Thus, for instance, a caustic soda solution or a soda solution may be injected. Preferably, however, a limewater solution is added to the solution used in the method according to the invention.

It is once more emphasized that the method according to the invention utilizes processes that are called undesirable - incrustation or scale formation - or processes used to avoid these undesirable processes - softening water.

The article Medical Applications of Calciumphosphate Bioceramics by K. de Groot in Journal of the Ceramic Society of Japan, 99 (1991), 943-953 shows that the optimum thickness for a coating layer on an implant is determined at the upper limit by the strength, the brittleness of the coating layer and at the lower limit by the fact that an apatite surface is decomposed in the body.

It has been shown that a thicker coating is more brittle and less strong than a thinner coating. Since, furthermore, thinner coatings more properly adhere to a substrate, it seems desirable to apply a thinnest possible coating layer.

On the other hand, apatite surfaces degrade in the body. Care must be taken that the layer is so thick that skeleton tissue can grow onto it. It is known that about 20 μm apatite a year are decomposed in the body. Besides, studies have shown that the role of hydroxyapatite coatings is essential, especially in the first year and in particular in the first month after application of an implant.

In a preferred embodiment of the method according to the invention a layer of bioactive material is deposited having a thickness in the range of 5 - 100 μm, and preferably in the range of 10 - 50 μm.

As stated above, the starting solution is preferably an aqueous solution of calcium ions which further comprises at least (hydrogen) carbonate ions and preferably phosphate ions

as well. In general, this aqueous solution will be weakly acid. In a preferred embodiment this solution also comprises fluoride ions. It is known that fluorapatite does not degrade under physiological conditions. Although traces of other elements may be present, the starting solution is preferably prepared with purest possible starting materials. Thus, for an aqueous solution the starting material is particularly aqua dest.

Finally, the invention relates to a new implant comprising a substrate material coated with a carbonate-containing calcium phosphate layer. During the production known implants coated with bioactive compounds are always subjected to a heat treatment (e.g., plasma formation of calcining steps). As a result of the known heat treatments all carbonate will always escape in the form of CO_2. According to the method of the invention it is now possible to apply carbonate-containing calcium phosphate coatings to implants.

The substrate used may be known implant materials. Excellent results are particularly obtained when the bioactive coating is applied to metal implants. Suitable materials comprise titanium, titanium alloys, stainless steel, and chromium-nickel-cobalt alloys. Besides, the concept of the method according to the invention may also be used for the production of bioactive bulk material for the formation of small implants, such as middle ear prostheses, by placing a graft material in the, preferably metastable, solution.

One of the great advantages of the method according to the invention over known methods is the absence of a heating step in which temperatures far above 100°C are reached (plasma formation or calcining step). This renders it possible to also coat synthetic substrates with a bioactive calcium salt, which can lead to new possibilities in the application of implants.

Example 1

An aqueous solution having 142 mM Na^+, 5 mM K^+, 2.5 mM Ca^{2+}, 147.8 mM Cl^-, 4.2 mM HCO_3^-, and 1 mM HPO_4^{2-} was prepared by

dissolving "reagent grade" NaCl, $NaHCO_3$, KCl, $K_2HPO_4 \cdot 3H_2O$, and $CaCl_2$ in distilled water. An implant of stainless steel was immersed in this solution, after which the solution was heated to 87°C. A carbonate-containing hydroxyapatite layer was deposited having a thickness in the range of 1 - 10 µm. This can be confirmed by FT-IR reflection analysis and SEM images.

Example 2

A stainless steel implant was placed in the solution prepared in Example 1. Then a 1 molar limewater solution was continuously fed to the solution. It was shown that a carbonate-containing hydroxyapatite layer was deposited at a rate of 2-3 µm/h. The deposited salt layer was considerably smoother than the layer obtained using the method according to Example 1.

CLAIMS

1. A method of coating an implant substrate with a bioactive material represented by the general formula $Ca_p(PO_4)_q(CO_3)_r(OH)_s$, in which $p \geq 1$ and q, r and $s \geq 0$, and in which $2p = 3q + 2r + s$, wherein said substrate, which is free of a coating of an organic polymer containing sulfonic or carboxyl groups, is placed in a solution in which at least calcium ions, preferably carbonate ions and, if required, phosphate ions are present, after which the bioactive material is precipitated from the solution on the substrate.

2. A method according to claim 1, wherein a bioactive material is precipitated in which the p/q ratio ranges between 1 and 2.

3. A method according to claim 1 or 2, wherein the solution used is an aqueous solution.

4. A method according to any of the preceding claims, wherein the solution is heated so as to precipitate the bioactive material on the substrate.

5. A method according to any of claims 1 - 3, wherein the substrate is heated so as to precipitate the bioactive material thereon.

6. A method according to any of claims 1 - 3, wherein a basic compound is added to the solution so as to precipitate the bioactive material on the substrate.

7. A method according to any of the preceding claims, wherein a layer of bioactive material having a thickness in the range of 5 - 100 μm is deposited.

8. A method according to any of the preceding claims, in which fluoride ions are also present in the solution.

9. An implantate comprising a substrate material coated with a carbonate-containing calcium phosphate layer.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/NL 94/00279

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61L27/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 450 939 (NORIAN) 9 October 1991 cited in the application see page 4, line 1 - line 23; claims 1-4 ---	1-4,6-9
A	EP,A,0 130 916 (SOCIETE EUROPEENNE DE PROPULSION) 9 January 1985 cited in the application see the whole document ---	1-3,5
A	WO,A,93 07912 (SHERWOOD MEDICAL) 29 April 1993 cited in the application see claims 9,16,18 ---	1-8
Y	WO,A,86 01726 (MERCK PATENT GESELLSCHAFT) 27 March 1986 see page 12, line 24 - line 35; claims 4-6,9; examples 3,4 --- -/--	1-8

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
24 February 1995	13. 03. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Peltre, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/NL 94/00279

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 389 713 (KYOTO UNIVERSITY) 3 October 1990 see page 3, line 42 - line 58; table 2 -----	1-8

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte onal Application No
PCT/NL 94/00279

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0450939	09-10-91	US-A-	5164187	17-11-92
		JP-A-	4224747	14-08-92
		US-A-	5188670	23-02-93
		US-A-	5279831	18-01-94
EP-A-0130916	09-01-85	FR-A-	2548011	04-01-85
		DE-A-	3467299	17-12-87
		JP-A-	60034449	22-02-85
		US-A-	4705694	10-11-87
WO-A-9307912	29-04-93	JP-A-	5103826	27-04-93
		AU-A-	2779792	21-05-93
WO-A-8601726	27-03-86	DE-C-	3433210	05-06-86
		EP-A,B	0193588	10-09-86
		JP-B-	5088148	21-12-93
		JP-T-	62500153	22-01-87
		US-A-	4917702	17-04-90
EP-A-0389713	03-10-90	JP-A-	2255515	16-10-90
		JP-B-	6029126	20-04-94
		DE-T-	68908158	25-11-93
		US-A-	5068122	26-11-91